Incidence and Clinical Features of Disease Progression in Adult Moyamoya Disease

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Background and Purpose—The progression of occlusive lesions in the major intracranial arteries was believed to be very rare in adult patients with moyamoya disease. The present study aims to clarify the incidence and clinical features of disease progression in adult moyamoya disease.

Methods—For the past 15 years, 120 adult Japanese patients were diagnosed with moyamoya disease. Of these, 63 patients were enrolled in this historical prospective cohort study on a total of 86 nonoperated hemispheres. All were followed up with a mean period of 73.6 months. MRI and magnetic resonance angiography were repeated every 6 to 12 months, and cerebral angiography was performed when disease progression was suspected on MRI and magnetic resonance angiography.

Results—Disease progression occurred in 15 of 86 nonoperated hemispheres (17.4% per hemisphere) or in 15 of 63 patients (23.8% per patient) during the follow-up period. Occlusive arterial lesions progressed in both anterior and posterior circulations, in both symptomatic and asymptomatic patients, and in both bilateral and unilateral types. Eight of 15 patients developed ischemic or hemorrhagic events in relation to disease progression. Multivariate analysis revealed that the odds ratio conferred by a male patient was 0.20 (95% CI, 0.04 to 0.97).

Conclusions—The incidence of disease progression in adult moyamoya disease is much higher than recognized before, and female patients may be at higher risk for it than male patients. Careful follow-up would be essential to prevent additional stroke occurrence in medically treated adult patients with moyamoya disease, even if they are asymptomatic or are diagnosed as having unilateral moyamoya disease. (***Stroke.* 2005;36:2148-2153.**)

Key Words: adult ■ cerebral ischemia ■ disease progression ■ moyamoya disease

Moyamoya disease is characterized by progressive occlusion of the bilateral carotid forks associated with a fine vascular network at the base of brain, the "moyamoya" vessels.[1] The posterior cerebral artery is also involved in ≈30% of patients with moyamoya disease.[2] Both children and adults develop moyamoya disease, but their clinical features often differ. Thus, although most pediatric patients develop transient ischemic attack (TIA) or cerebral infarction, about half of adult patients experience intracranial bleeding. In addition, the occlusive lesions in the carotid forks frequently progress in pediatric patients, although it is believed quite rare in adult patients.[3,4] Only 8 cases have previously been reported to demonstrate the progression of occlusive lesions in adult patients with moyamoya disease.[3,5–11] However, there is no report that precisely denoted the incidence and features of stage progression in a large population of adult patients with moyamoya disease.

On the other hand, the recent development of a noninvasive diagnostic technique, magnetic resonance angiography (MRA), has clarified that the prevalence of asymptomatic adult patients with moyamoya disease is much higher than considered before.[12] However, the guideline for the management of asymptomatic adult moyamoya disease has not been established, even in Japan.[12–14] The natural course of adult moyamoya disease should also be elucidated in order to determine appropriate therapeutic strategies for asymptomatic patients. Therefore, in this study, we aimed to clarify the incidence and clinical features of disease progression in adult moyamoya disease.

Materials and Methods

Patients and Follow-Up

This study included 120 adult patients who were diagnosed with moyamoya disease at Hokkaido University Hospital and its affiliate hospitals in Sapporo between 1990 and 2004. All of them were >20 years of age at onset and were diagnosed with moyamoya disease based on the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan. Of these 120 patients, 6 (5%) were deceased because of severe intracranial bleeding within 1 month after the onset. Using

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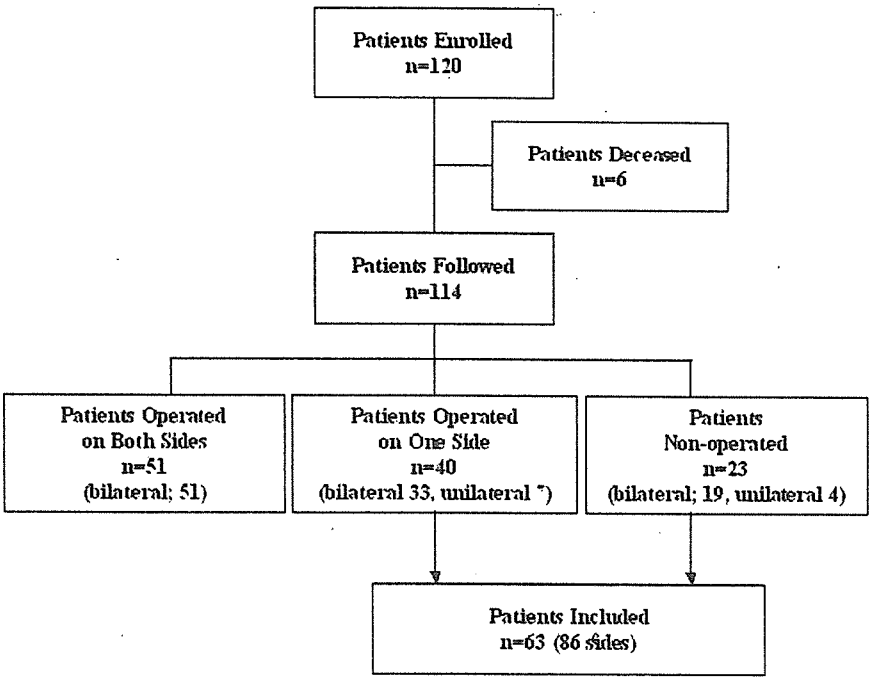

Figure 1. Diagram of adult patients with moyamoya disease included in this study.

^{133}xenon or ^{123}I-IMP single photon emission computed tomography, cerebral blood flow and its reactivity to acetazolamide were quantitatively measured in all of the patients at least 4 weeks after the onset.[15–18] The involved hemisphere was considered as the candidate for surgical revascularization when it had impaired reactivity to acetazolamide.[15–18] As a result, surgical revascularization was performed on 142 sides of 91 patients. Fifty-one patients underwent surgical revascularization on both sides. On the other hand, 40 patients underwent it on 1 side. Surgical procedures included superficial temporal artery to middle cerebral artery anastomosis combined with encephalo-myo-synangiosis or encephalo-duro-arterio-myo-synangiosis in all of these patients.[19] The other 23 patients were medically treated according to the above-mentioned criteria or patients' request. Therefore, we enrolled 63 patients in this study, for a total of 86 nonoperated sides, and evaluated their natural course (Figure 1). There were 23 male and 40 female patients. Of these, 52 patients were diagnosed with typical "bilateral" moyamoya disease (definite cases). The other 11 patients were diagnosed with "unilateral" moyamoya disease (probable cases). Their mean age at onset was 46.7±10.8 years. Their clinical type included ischemic type in 28 patients, bleeding type in 24, and asymptomatic in 11.

All 63 patients included in the present study were followed up in the outpatient clinic at Hokkaido University Hospital or its affiliate hospitals. The mean follow-up period was 73.6±49.0 months, ranging from 7 to 181 months. Both MRI and MRA were performed every 6 or 12 months, using a 1.5-T whole-body magnetic resonance imager. When the progression of the occlusive lesion in the major intracranial arteries was suspected, digital subtraction angiography was performed to verify it. Occlusive lesions in the carotid forks were graded according to Suzuki's angiographical staging.[1]

Statistical Analysis

To clarify the predictors of disease progression in adult moyamoya disease, primary comparisons were performed between the patients with and without disease progression. Categorical variables were compared by using a χ^2 test. Continuous variables were expressed as percentage or as mean±SD, and were compared by using the unpaired Student t test. Differences were considered to be statistically significant if the P value was <0.05. Subsequently, a multivariate logistic regression model was conducted to test the effect of gender, onset age, disease type, symptoms at onset, and previous surgery on disease progression. The statistical level of significance was also set at $P<0.05$. Statistical analysis was completed with StatView version 5.0 (SAS Institute Inc.).[20]

Results

Characteristics of Stage Progression

During follow-up periods, the occlusive lesions in the major intracranial arteries progressed in 15 of 86 sides (17.4% per hemisphere) or in 15 of 63 patients (23.8% per patient). Disease progression was verified in 2 men and 13 women, and their age at onset was 46.9±8.2 years (range, 32 to 60 years). Their symptoms at onset included TIA or cerebral infarction in 9 patients and intracranial bleeding in 4. The remaining 2 patients were asymptomatic when they were diagnosed with moyamoya disease.

Disease progression occurred in 4 of 11 patients (36.4%) with unilateral moyamoya disease and in 11 of 52 patients (21.2%) with bilateral moyamoya disease. Thus, the carotid fork of the contralateral side was involved in 4 patients with unilateral moyamoya disease, which meant progression from unilateral to bilateral type. The interval between their onset and disease progression varied from 1.5 to 8 years (60.0±36.3 months). All of the patients were women. In relation to the progression from unilateral to bilateral type, TIA or intracranial bleeding occurred in 3 patients, and a single photon emission tomography study revealed the deterioration of cerebral hemodynamics in another (case 3). All of them underwent additional bypass surgery (Table 1). On the other hands, 8 of 52 patients with bilateral moyamoya disease showed the progression of the occlusive lesion in the carotid fork. The other 3 patients with bilateral moyamoya disease developed an additional occlusive lesion in the posterior cerebral artery (PCA) during follow-up periods (Table 2). The interval between their onset and disease progression was 28.4±26.3 months, ranging from 1 month to 8 years, and was significantly shorter in patients with bilateral moyamoya

TABLE 1. Clinical Features of 4 Adult Patients Who Showed the Progression From Unilateral to Bilateral Moyamoya Disease

		Onset			Progression		
Case	Age/Gender	Symptom	Involved Side	Bypass Surgery	Symptom	Additional Side	Interval (yr)
1	52F	Bleeding	Rt	None	Bleeding	Lt	7
2	44F	Infarct	Lt	Lt	TIA	Rt	3.5
3	33F	Bleeding	Rt	Rt	None	Lt	8
4	45F	TIA	Lt	Lt	TIA	Rt	1.5

Rt indicates right; Lt, left.

disease than in those with unilateral moyamoya disease (P=0.0123). In relation to the disease progression, TIA or cerebral infarction occurred in 5 patients, and cerebral hemodynamics worsened in another 2 (cases 5 and 14). Subsequently, 8 patients underwent bypass surgery.

Independent Predictor of Disease Progression

The effects of various clinical factors on disease progression are shown in Table 3. The patients with and without disease progression were categorized into the progression group (n=15) and stable group (n=48), respectively. As the results of univariate analysis, there was no significant difference in onset age, disease type, symptoms at onset, and previous bypass surgery between the 2 groups. However, disease progression was noted in 13 of 40 female patients (32.5%), but in 2 of 23 male patients (8.7%), revealing that the incidence of disease progression was significantly higher in female patients than in male patients (χ^2 test, P=0.0327).

As the next step, multivariate logistic regression analysis showed that patients' gender was an independent predictor of disease progression during follow-up periods (P=0.0463). The odds ratio conferred by a male patient was 0.20 (95% CI, 0.04 to 0.97) for disease progression (Table 3).

Illustrative Cases

Case 14

A 50-year-old female experienced minor head injury because of a traffic accident in March 2001. Because brain MRI and MRA studies strongly suggested the presence of moyamoya disease, cerebral angiography was performed. Right carotid angiography showed the stenosis of the right anterior cerebral artery (Figure 2a). The left cerebral angiography revealed marked stenosis of the left internal carotid artery and middle cerebral artery associated with mild dilatation of the lenticulostriate arteries (Figure 2b). Although she was still asymptomatic, follow-up cerebral angiography in March 2004 showed progression of an occlusive lesion on the left side (Figure 2c). Single photon emission tomography studies also revealed the reduction of cerebral blood flow and its reactivity to acetazolamide. She underwent superficial temporal artery to middle cerebral artery anastomosis and encephalo-duro-arterio-myo-synangiosis. Postoperative course was uneventful.

Case 15

A 56-year-old female was admitted to our hospital because of a severe headache and consciousness disturbance in March 1996. Plain computed tomography scans revealed intracerebral hematoma in the right putamen (Figure 3a). Cerebral angiography on admission showed the marked stenosis of the bilateral carotid forks. The posterior cerebral arteries were intact. She was diagnosed with moyamoya disease. She completely recovered and was medically followed up because she and her family did not want surgical revascularization. The brain MRI and MRA were annually repeated at an outpatient clinic. Although the posterior cerebral arteries

TABLE 2. Clinical Features of 11 Adult Patients With Bilateral Moyamoya Disease Showing the Progression of Occlusive Lesion in the Major Intracranial Arteries

		Onset			Progression		
Case	Age/Gender	Symptom	Symptomatic Side	Bypass Surgery	Symptom	Progressed Lesion	Interval
5	53F	TIA	Rt	Rt	None	Lt PCA	2 y
6	37F	TIA	Lt	Lt	Infarct	Rt (2 → 4)	2 y
7	50F	TIA	Rt	Rt	None	Lt (2 → 4)	3 y
8	55M	None		None	Infarct	Lt (2 → 4)	3 y
9	48M	Bleeding	Lt	None	Infarct	Lt (3 → 4)	1 mo
10	32F	TIA	Lt	None	None	Lt (2 → 3)	3 mo
11	50F	Infarct	Lt	None	None	Lt (2 → 3)	9 mo
12	60F	TIA	Rt	Rt	Infarct	Lt PCA	11 mo
13	41F	TIA	Lt	None	TIA	Rt (3 → 4)	3 y
14	50F	None		None	None	Lt (3 → 4)	3 y
15	54F	Bleeding	Rt	None	None	Rt PCA	8 y

Occlusive lesions in the carotid forks were graded according to Suzuki's angiographical staging; Rt indicates right; Lt, left.

TABLE 3. Clinical Features of the Patients With Stage Progression of Adult Moyamoya Disease (Progression Group) and Without (Stable Group)

Variables	Progression Group	Stable Group	Univariate Analysis	Multivariate Analysis	Odds Ratio (95% CI)
No. of patients	15	48			
Gender					
Male	2	21	P=0.0327	P=0.0463	0.20 (0.04–0.97)
Female	13	27			
Age at onset (y)	46.9±8.2	47.0±9.9	P=0.9754		
Disease type					
Bilateral	11	41	P=0.2819		
Unilateral	4	7			
Symptoms at onset					
Ischemia	9	19	P=0.3793		
Bleeding	4	20			
Asymptomatic	2	9			
Bypass surgery					
Yes	7	33	P=0.1210		
No	8	15			

Continuous data are expressed as mean±SD.

were intact in March 2004 (Figure 3b), a marked stenosis developed in the right posterior cerebral artery in March 2005 (Figure 3c).

Discussion

This study is the first to focus on clinical manifestations of the progression in the major intracranial arteries in a large population of patients with adult moyamoya disease. The results clearly showed that the incidence of disease progression was ≈20% in adult patients with moyamoya disease, which is higher than what was considered before. Disease progression occurred in both unilateral and bilateral moyamoya disease, in both anterior and posterior circulation, and in both symptomatic and asymptomatic patients. An ischemic or hemorrhagic episode was noted in more than half of patients when the occlusive lesions progressed. Multivariate analysis revealed that female patients had a higher risk of disease progression than male patients.

As described above, the disease progression in adult moyamoya disease has previously been recognized as very rare, and 8 patients have been reported to exhibit it as case reports.[3,5–11] In addition, Kawano et al[21] reported 4 adult patients who showed progression from unilateral to bilateral type in their series of 64 cases with unilateral moyamoya disease, although their clinical data were limited. Clinical information of these 12 patients is summarized in Table 4. Thus, the occlusive lesions in the carotid fork advanced in both sides or in the nonoperated side in 4 adult patients with bilateral moyamoya disease.[3,6–8] In addition, unilateral moyamoya disease has been reported to progress to bilateral type in 8 adult patients.[5,9–11,21] As shown in this study, disease progression occurred within 1 year after the onset in 2 of 4 patients with bilateral moyamoya disease, whereas it occurred 1 to 6 years after the onset in patients with unilateral moyamoya disease. When analyzing 8 patients with sufficient clinical information (case 1 to 5 and 10 to 12), 3 developed ischemic or hemorrhagic episode because of disease progression. Gender difference was not observed in these 8 cases, which is different from the present result. It may result from the difference of patients' background among the studies. However, Kawano et al[21] reported female predominance in patients with unilateral moyamoya disease showing progression to a bilateral type, correlating well with the present result.

Unilateral moyamoya disease accounts for ≈20% of all of the moyamoya disease in Japan.[22] According to previous surveys,

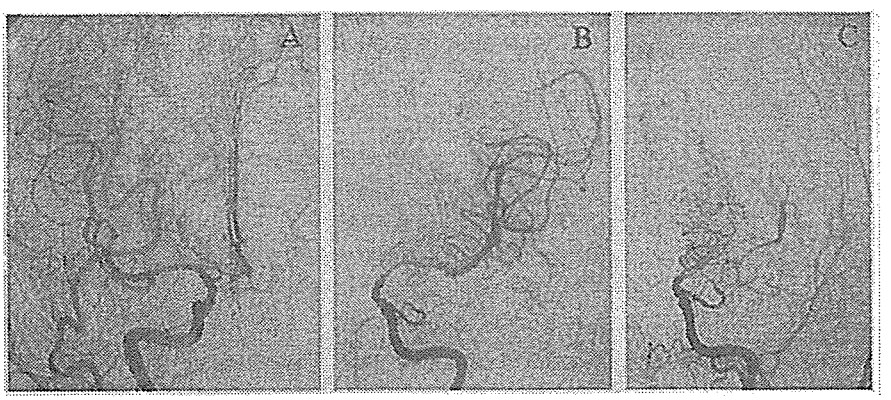

Figure 2. Right (a) and left internal carotid angiograms (b and c) of a 50-year-old woman (case 14), showing progression of an occlusive lesion in the left carotid fork during 3-year follow up (b and c).

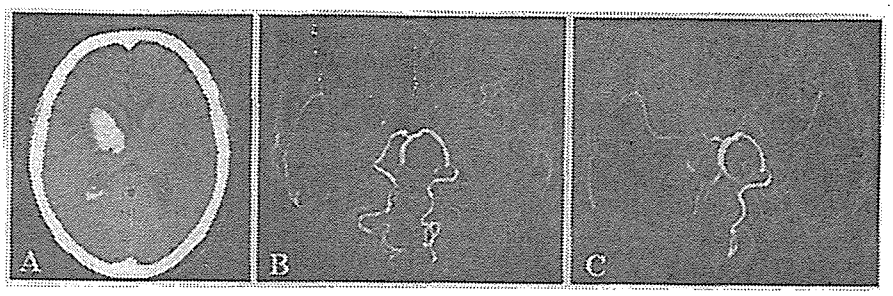

Figure 3. Plain computed tomography (a) and MRA (b and c) of a 56-year-old woman (case 15), showing the development of an occlusive lesion in the right posterior cerebral artery between March 2004 (b) and March 2005 (c).

unilateral moyamoya disease has been recognized as stable in adults.[21,23,24] However, this study revealed that about one-third of patients progressed to the typical bilateral type. The discrepancy may result from the difference in follow-up periods. Thus, mean follow-up periods were within 3 years in previous studies.[21,23,24] On the other hand, the patients included in this study were followed up for a mean period of ≈6 years. Because the interval between initial diagnosis and disease progression is significantly longer in unilateral moyamoya disease than in the bilateral type, long-term follow-up would be essential to discuss the prognosis of unilateral moyamoya disease. Indeed, disease progression was confirmed 7 to 8 years after the initial diagnosis in 2 patients (cases 1 and 3, Table 1).

In this study, 3 patients developed additional occlusive lesions in the PCA during follow-up periods. To our best knowledge, there is no report describing the phenomenon in adult moyamoya disease. The development of additional PCA lesions implies the increased risk for recurrent ischemic stroke, because the PCA is playing an important role as a major collateral circulation in moyamoya disease as pointed out before.[2,25,26] In this study, cerebral infarction occurred in 1 patient, and cerebral hemodynamics deteriorated in another 2. Therefore, the importance of carefully observing the whole intracranial arteries should be remembered during follow-up.

Noninvasive examinations using MRI and MRA have revealed that the incidence of asymptomatic moyamoya disease is much higher than believed before.[12] However, the prognosis of asymptomatic patients is still unclear, and the standardized strategy for them has not been established.[12–14] This study revealed that the occlusive arterial lesions advanced in 2 of 11 asymptomatic patients (18.2%) during 3 years, leading to cerebral infarction (case 8) or disturbed cerebral hemodynamics (case 14). The findings should be taken into consideration when establishing the management guideline for asymptomatic patients with moyamoya disease, although additional survey would be necessary on the basis of a larger population of asymptomatic patients. Furthermore, MRI and MRA studies at outpatient clinics could accurately detect disease progression before recurrent onsets including TIA, cerebral infarction, and intracranial bleeding in 7 of 15 patients, suggesting the importance of continuous imaging studies.

Based on multivariate analysis in this study, female gender may be a significant predictor of disease progression in adult moyamoya disease. None of the other factors were related to disease progression. Previous epidemiological surveys have shown that a male-to-female ratio of moyamoya disease is ≈1:1.8,[27] suggesting the female predominance in moyamoya disease. Furthermore, female predominance is more pronounced in familial moyamoya disease. Thus, Kanai et al[28] reported that a male-to-female ratio in familial moyamoya disease was 1:3.3. A recent study[29] also showed that male-to-female ratios were 1:5 and 1:1.6 in familial and sporadic cases, respectively, indicating

TABLE 4. Summary of Clinical Features in 12 Reported Case With Moyamoya Disease Showing Progression of Occlusive Arterial Lesions

			Onset	Progression			
Initial Diagnosis	Age	Gender	Symptom	Side	Symptom	Interval	Authors (Year)
Bilateral moyamoya disease							
1	25	M	Infarct	Both sides	None	17 y	Takeshita et al (1995)[6]
2	56	F	Infarct	Nonoperated side	None	5 mo	Shirane et al (1999)[3]
3	47	F	Infarct	Nonoperated side	TIA	1 mo	Oka et al (2000)[8]
4	37	M	Infarct	Both sides	Bleeding	4 y	Tomida et al (2000)[7]
Unilateral moyamoya disease							
5	30	F	TIA	Both sides	None	4 y	Aoki et al (1989)[11]
6	27		TIA	Noninvolved side		1 y	Kawano et al (1994)[21]
7	30		TIA	Noninvolved side		6 y	
8	41		TIA	Noninvolved side		5 y	
9	63		Bleeding	Noninvolved side		1 y	
10	38	M	Infarct	Noninvolved side	Bleeding	2.5 y	Wanifuchi et al (1996)[10]
11	54	M	Infarct	Noninvolved side	None	4 y	Fujiwara et al (1997)[5]
12	21	F	Infarct	Noninvolved side	None	2.5 y	Kagawa et al (2004)[9]

enhanced female predominance in familial moyamoya disease. The results strongly suggest that female gender may be highly susceptible to the unknown factors causing moyamoya disease and may promote disease progression more easily.

Recently, the prospective, randomized clinical trial has been accepted to provide the highest level of evidence. The present study has some problems for evidence-based medicine. Thus, this study has bias in the patient selection. The patients who underwent bypass surgery on both sides were excluded, because it is well known that occlusive lesions in the carotid fork rapidly progress and often result in complete occlusion when surgical collaterals start to supply enough blood flow after surgery.[30–32] As a result, this study included the patients who underwent bypass surgery on one side and those who were medically treated and observed their natural course. Therefore, we cannot exclude the possibility that the present results are diluted because less severe patients were included in this study.

In conclusion, the process of occlusive arterial change in adult moyamoya disease is still active. Disease progression can occur in both anterior and posterior circulations, in both symptomatic and asymptomatic patients, and in both unilateral and bilateral types. Careful and long-term neurological and radiological follow-up would be essential in adult patients with moyamoya disease to prevent additional stroke events and to improve their outcome.

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Abstract *Objects:* This study aims to clarify the genetic background of moyamoya disease by comparing clinical features between familial and sporadic cases to reveal the responsible genes for familial moyamoya disease. *Methods:* This study included 155 Japanese patients with moyamoya disease, which included 24 familial cases (10 family pedigrees) and 131 sporadic cases. Clinical features were compared between the familial and sporadic cases. *Results and conclusion:* A female preponderance was significantly more prominent in the familial than in the sporadic group (P=0.0421). Mean age at onset was significantly lower in familial than in sporadic cases (P=0.004). In eight parent–offspring pairs, mean age at onset was significantly lower in the second than in the first generation (P<0.0001). These results suggest that familial moyamoya disease is associated with genetic anticipation and female predominance and that a genetic analysis study focused on expanded triplet repeats may clarify the pathogenesis of the disease.

Keywords Moyamoya disease · Genetics · Anticipation · Familial case · Age at onset · Female predominance · Triplet repeat

Introduction

Moyamoya disease (spontaneous occlusion of the circle of Willis) is characterized by a progressive stenosis or occlusion of the terminal portions of the bilateral internal carotid arteries associated with abnormal vascular network at the base of the brain ("moyamoya" vessels; [19]). Clinically, of special interest is that moyamoya disease occurs in both children and adults. Most pediatric patients develop transient ischemic attack (TIA) or cerebral infarction, whereas adult patients more frequently suffer intracranial hemorrhage. The man-to-woman ratio is 1:1.8 [22].

The pathogenesis of moyamoya disease is still unknown. Several epidemiological studies suggest that infection in the head and neck regions may be related to moyamoya disease, although a certain infectious pathogen has not been determined [23]. Alternatively, specific cytokines such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factors have been proposed as pathogenetic factors for moyamoya disease because these substances are detected at high levels in the cerebrospinal fluid and the involved arteries of patients with moyamoya disease [20, 26]. Furthermore, it has been widely accepted that some genetic factors may play an important role in the pathogenesis of moyamoya disease. The hypothesis is based on the facts that familial occurrence has been recognized in approximately 10–15% of patients and that the incidence of moyamoya disease is much higher in Far Eastern than in western countries [24]. Thus, according to recent literature review, 172 familial cases of 76 pedigrees have been reported. Of these, 38 parent–offspring pairs of 16 pedigrees and 128 sibling pairs of 51 pedigrees have been described [15]. Compared with the general population, first- or second-degree relatives are known to have a 30- to 40-fold significantly increased risk of moyamoya disease [10]. Identical twins associated with

moyamoya disease have also been reported [11]. The incidence is 0.35 per 100,000 in Japan, but only 201 and 105 patients have been reported from Europe and USA, respectively, between 1972 and 1989 [4]. The incidence is higher in Japanese population than in the Hawaiian population [5].

Clinical studies of familial cases have suggested that moyamoya disease is most likely inherited in a polygenic mode or in an autosomal-dominant fashion with a low penetrance. Microsatellite linkage analysis has recently identified the genetic loci on chromosomes 3, 6, and 17 [8, 9, 25]. However, the responsible genes have not been identified yet [15].

Based on these considerations, the present study aims to facilitate the transition from linkage analyses to the identification of responsible genes by analyzing clinical manifestations among familial and sporadic cases of moyamoya disease.

Materials and methods

Patients

The current study included 155 patients with moyamoya disease. Of these, 141 were admitted to our hospital between 1969 and 2002 and were diagnosed as having moyamoya disease on cerebral angiography based on the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan. All patients were Japanese and were residents of Hokkaido Island, a northern part of Japan. All of them presented with TIA, cerebral infarction, or intracranial hemorrhage. When they were diagnosed as having moyamoya disease, their family history was precisely evaluated, and the members of their family underwent cerebral angiography or magnetic resonance angiography (MRA) when they had at least one episode suggesting the symptoms of moyamoya disease or when they strongly desired MRI/MRA examination as a screening tool. As a result, an additional 14 patients were diagnosed as having moyamoya disease, bringing the total number of patients included in this study to 155. Of these, 110 patients were categorized as definite cases and the other 45 as probable cases. This study did not include quasi-moyamoya cases.

To characterize the clinical features in familial moyamoya disease, the authors compared the gender, age at onset, and symptoms at onset of the patients between the familial and sporadic cases.

Statistical analysis

All data were expressed as mean±SD. Categorical variables were compared using the chi-square test. Continuous variables were compared using a two-tailed unpaired Student's *t* test. The cumulative onset free-survival rate was compared between the studied groups using the Kaplan–Meier method and Mantel–Cox log-rank statistics. Differences were considered to be statistically significant if the *P* value was <0.05. All statistical analyses were performed using StatView ver 5.0 (SAS Institute Inc., USA).

Results

Familial and sporadic moyamoya disease

Of the 155 patients included in this study, familial occurrence was observed in 24 patients of 10 pedigrees (familial group). The other 131 patients were sporadic cases (sporadic group). The clinical features of both groups are summarized in Table 1.

There were 4 men and 20 women in the familial group, while there were 50 men and 81 women in the sporadic group. Therefore, a female preponderance was significantly more prominent in the familial than in the sporadic group (chi-square test, P=0.0421). Age at onset ranged from 1 to 36 years (11.8±11.7 years) in the familial group and from 1 to 78 years (30.0±20.9 years) in the sporadic group. As a result, mean age at onset was significantly lower in the familial than in the sporadic group (unpaired *t* test, P=0.0043). Kaplan–Meier analysis and Mantel–Cox log-rank statistics also showed that age at onset was significantly lower in the familial than in the sporadic group (Fig. 1; P<0.0001).

Table 1 Summary of clinical characteristics in familial and sporadic group of moyamoya disease

	Familial group	Sporadic group	Significance
n	24	131	
Gender (male/female)	4:20	50:81	P=0.0421
Age at onset (years)	11.8±11.7	30.0±20.9	P=0.0043
Clinical diagnosis at onset	TIA: 19	TIA: 43	P<0.0001
	Cerebral infarct: 0	Cerebral infarct: 48	
	Intracranial bleeding: 3	Intracranial bleeding: 37	
	None: 2	None: 3	

TIA Transient ischemic attack

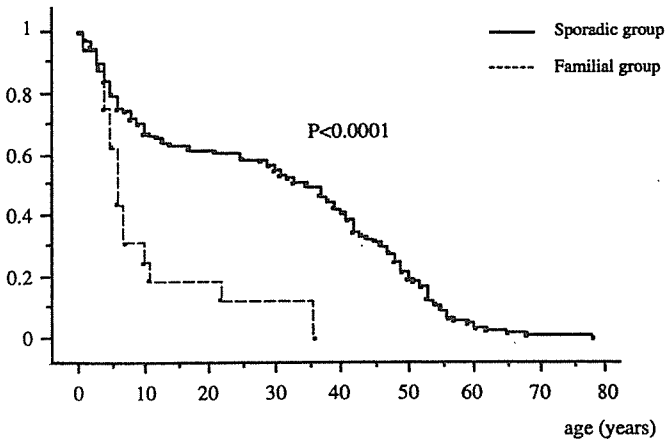

Fig. 1 Graph showing the age at onset in familial and sporadic cases with moyamoya disease. Kaplan–Meier analysis reveals that the age at onset is significantly lower in familial than in sporadic group

In the familial group (n=24), clinical symptoms at onset included TIA in 19 patients (79.2%), intracranial hemorrhage in 3 (12.5%), and none in 2 (8.3%). On the other hand, in the sporadic group (n=131), clinical symptoms at onset included TIA in 43 patients (32.8%), completed ischemic stroke in 48 (36.6%), intracranial hemorrhage in 37 (28.2%), and none in 3 (2.3%). Thus, the symptoms at onset were significantly different between the two groups (chi-square test, P<0.0001), and completed ischemic stroke developed more often in the sporadic than in the familial group.

Clinical features of familial moyamoya disease

As a next step, the authors analyzed the clinical features of familial moyamoya disease to characterize their genetic properties. Of 10 pedigrees, there were eight parent–offspring pairs, all of which were mother–offspring pairs. There were four sibling pairs, one of which was twins (Fig. 2). Of the eight parent–offspring pairs, seven parents were symptomatic and one was asymptomatic. The seven symptomatic parents presented with the symptoms related to moyamoya disease when they were 22 to 36 years old (30.7±7.5 years). On the other hand, their children presented with the symptom when they were 5 to 11 years old (7.2±2.7 years). Thus, mean age at onset was significantly lower in the second than in the first generation (unpaired t test, P<0.0001). Of the eight parents, symptoms at onset included TIA in five and intracranial hemorrhage in three, whereas all of their children experienced TIA at onset.

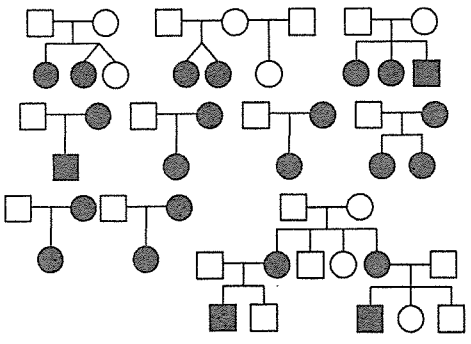

Fig. 2 Ten pedigrees of familial moyamoya disease included in the present study

Discussion

Epidemiological features of familial moyamoya disease

The current study demonstrates several clinical features of familial moyamoya disease. First, the female preponderance in sporadic moyamoya disease is overrepresented in familial moyamoya disease, although the bias in the data sample cannot be excluded. Furthermore, a significant mother–offspring transmission is observed in the present study. The man-to-woman ratio of moyamoya disease is generally known as 1:1.8 [22]. However, a previous survey of familial moyamoya disease has also shown more pronounced female predominance, that is, 1:3.3 [10], consistent with the present result. The authors have recently reviewed previous literature on familial moyamoya disease and found 16 parent–offspring pairs of moyamoya disease [14]. There are 5 men and 11 women in the first generation, whereas there are 8 boys and 12 girls in the second generation. These clinical findings strongly suggest that women are highly susceptible to some genetic factors of familial moyamoya disease. Otherwise, the unknown genetic factors responsible for familial moyamoya disease might have some different effects on the gender. No reports have revealed that familial moyamoya disease is related with the X or Y chromosome. The responsible gene of the disease may exhibit a different pattern of expression according to gender. Recent studies have revealed that the methylation pattern of CpG island differs between genders and that the malfunction of methylation reflects the pathogenesis of certain genetic diseases such as Prader–Willi syndrome and Angelman syndrome [13].

Second, by the use of unpaired Student's t test and Kaplan–Meier analysis, this study indicates that mean age at onset is significantly lower in familial than in sporadic moyamoya disease. Previous clinical studies have revealed a similar result in some inheritable cerebrovascular or neurological disorders. Familial subarachnoid hemorrhage (SAH) is characterized, in comparison with SAH from sporadic aneurysms, by an earlier age at the time of SAH

[2, 12, 16]. A similar phenomenon has been observed in familial migraine and cluster headache [17, 21]. These findings seem to suggest that genetic factors affect age at onset of familial moyamoya disease. The patients in the sporadic group more often present with cerebral infarct and intracranial hemorrhage than do those in the familial group (Table 1). The difference most likely results from the finding that mean age at onset is significantly higher in the sporadic than in the familial group.

Third, the current study reveals that mean age at onset is significantly lower in the second than in the first generation among the eight parent–offspring pairs. These results are the same with that of a recent literature review on familial moyamoya disease. Thus, the parent–offspring pairs of 16 pedigrees have previously been reported. Mean age at onset of the 16 parents is significantly higher than that of their 20 children, 39.5±12.8 and 12.7±8.0 years, respectively ($P<0.0001$; [15]). These results strongly suggest that anticipation may be closely associated with familial moyamoya disease.

Anticipation and expansion of repeat sequence

The clinical phenomenon of decreasing age at onset and/or increasing severity of symptoms of a disease in successive generations within a pedigree has been termed anticipation [1]. In total, 73 familial disorders have been reported to be linked to anticipation. Of these, responsible genes have previously been clarified in 20 familial disorders, most of which are neurological or neuropsychiatric disorders, such as myotonic dystrophy and Huntington's disease. Recent studies have strongly suggested that anticipation is caused by pathogenic unstable triplet repeat. In many of these disorders, repeat size correlates with severity and inversely with age at onset rather than penetrance. As the repeats tend to expand during transmission between generations, the age at onset tends to decrease and the severity tends to increase. This instability has led to the description of pathogenic repeat sequences as dynamic mutations [7, 18].

Of the eight parent–offspring pairs in the present study, all were maternal inheritance. There is increasing evidence that imprinting phenomenon may be associated with anticipation in some familial neurological disorders, including Huntington's disease. Genomic imprinting has been defined as "the differential expression of genetic material, at either a chromosome or allelic level, depending on whether the genetic material has come from the male or female parent" [6]. Previous studies have suggested that the methylation of CpG island that often functions as a strong promoter plays a central role in genomic imprinting [6]. Therefore, genomic imprinting may also affect the predominance of maternal inheritance in familial moyamoya disease.

Limitation of the current study

As described above, the responsible genes for familial moyamoya disease have not been determined, although microsatellite linkage analyses have shown the genetic loci on chromosomes 3, 6, and 17 [8, 9, 25]. Indeed, positional cloning analysis has failed to identify the possible genes [15]. Therefore, the present results can be a guiding principle in research efforts for elucidating the genes.

The present study is the first attempt to statistically analyze the clinical features of familial moyamoya disease and strongly suggests the association of anticipation. Of course, however, it should be reminded that the signs of anticipation may be attributed to several sampling and observation biases, including the tendency to select the parents with late onset and the offspring with early onset [3]. Another possible bias that may mimic anticipation can result from shared environmental factors because the affected individuals within families are not widely distributed geographically and across time. Therefore, a larger sample size of familial moyamoya disease would be necessary to minimize all possible biases, verifying the present results.

Another difficulty should also be taken into consideration in analyzing the clinical manifestations of familial moyamoya disease. Thus, only 40 years has passed since moyamoya disease was identified as a clinical entity [19], and it is very difficult to obtain accurate medical records of three- or four-generation families with moyamoya disease. A prospective follow-up study over several generations within families may clarify the clinical feature of familial moyamoya disease.

Conclusion

In this study, the authors statistically analyzed the clinical features of familial and sporadic cases of moyamoya disease. The results strongly suggest that anticipation may be closely related to familial moyamoya disease, although further studies are necessary. The present results may shed light on future research for identifying the genes responsible for familial moyamoya disease.

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Survival and differentiation of neural progenitor cells derived from embryonic stem cells and transplanted into ischemic brain

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Object. Cell replacement therapy including the use of embryonic stem cells (ESCs) may represent a novel treatment for damage from stroke. In this study, the authors transplanted neural progenitor cells (NPCs) derived from ESCs into ischemic brain and analyzed their survival and differentiation.

Methods. Multipotential NPCs were generated from ESCs by using the stromal cell–derived inducing activity method. These cells could differentiate in vitro into neurons, glia, and oligodendrocytes, thus revealing them to be neural stem cells. The NPCs were then transplanted into ischemic brain. At 2 weeks postischemia, the transplanted cells occupied 18.8 ± 2.5% of the hemispheric area; by 4 weeks postischemia, 26.5 ± 4% of the hemisphere. At 4 weeks after transplantation, green fluorescent protein (GFP)–positive transplanted cells showed mature neuronal morphological features. The authors also investigated the expression of differentiation markers and various neurotransmitters. Transplanted cells were immunopositive for neuronal nuclei, β-tubulin-III, and glial fibrillary acidic protein. Of the GFP-positive cells, 33.3 ± 11.5% were positive for glutamate decarboxylase, 13.3 ± 5.8% for glutamate, 2.1 ± 2.5% for tyrosine hydroxylase, 1.8 ± 2% for serotonin, and 0.4 ± 0.2% for choline acetyltransferase.

Conclusions. The authors confirmed the survival and differentiation of ESC-derived NPCs transplanted into the ischemic brain. Surviving transplanted cells expressed several neural markers and neurotransmitters. These findings indicate that these cells can function in the brain.

KEY WORDS • **neural progenitor cell** • **embryonic stem cell** • **brain ischemia** • **stroke** • **mouse**

STROKE affects millions of people worldwide, with more than 500,000 new patients per year in the US alone. Although fewer than one third of strokes are fatal, approximately 60% of patients show significant residual impairments and the prevalence of stroke-related morbidity is expected to increase as the population ages because there is no therapy to reverse these effects. Cell replacement therapy, including the use of ESCs,[8] neural stem cells,[19,20,23,26,29] and bone marrow stromal cells,[3,6,7,15,16,32] may represent a novel treatment for stroke damage.[4,13]

Embryonic stem cells can be expanded to large numbers while maintaining their potential to differentiate into various somatic cell types of the three germ layers, and the in vitro differentiation of ESCs thus can provide donor cells for transplantation therapies. Indeed, ESCs have been found to differentiate in vitro into many clinically relevant cell types, including hematopoietic cells, cardiomyocytes, insulin-secreting cells, neurons, and glia.[4,13] Following transplantation into the central nervous system, ESC-derived neural precursors have been shown to integrate into host tissue and, in some cases, to promote functional improvement.[8] After brain ischemia, many types of cells are lost, including neurons, glia, and oligodendrocytes. It is hoped that NPCs can produce replacements.[26,31] Recently, Kawasaki and colleagues[12] reported that the SDIA method could easily produce NPCs from ESCs. In the present study, we generated NPCs from ESCs, expanded them as neurospheres, and transplanted them into the ischemic brain. To our knowledge, this is the first report on the use of ESC-derived neurons for transplantation into the ischemic brain.

Abbreviations used in this paper: ChAT = choline acetyltransferase; CNPase = cyclic nucleotide phosphodiesterase; ESC = embryonic stem cell; GAD = glutamate decarboxylase; GalC = galactocerebroside; GFAP = glial fibrillary acidic protein; GFP = green fluorescent protein; LIF = leukemia inhibitory factor; MCA = middle cerebral artery; NeuN = neuronal nuclei; NPC = neural progenitor cell; PBS = phosphate-buffered saline; rCBF = regional cerebral blood flow; SDIA = stromal cell–derived inducing activity; TH = tyrosine hydroxylase; TuJ1 = β-tubulin-III.

Materials and Methods

Induction of Neural Differentiation of ESCs

Undifferentiated murine ESCs (G4-2) were maintained on gelatin-coated dishes in Glasgow minimum essential medium (Sigma, St.

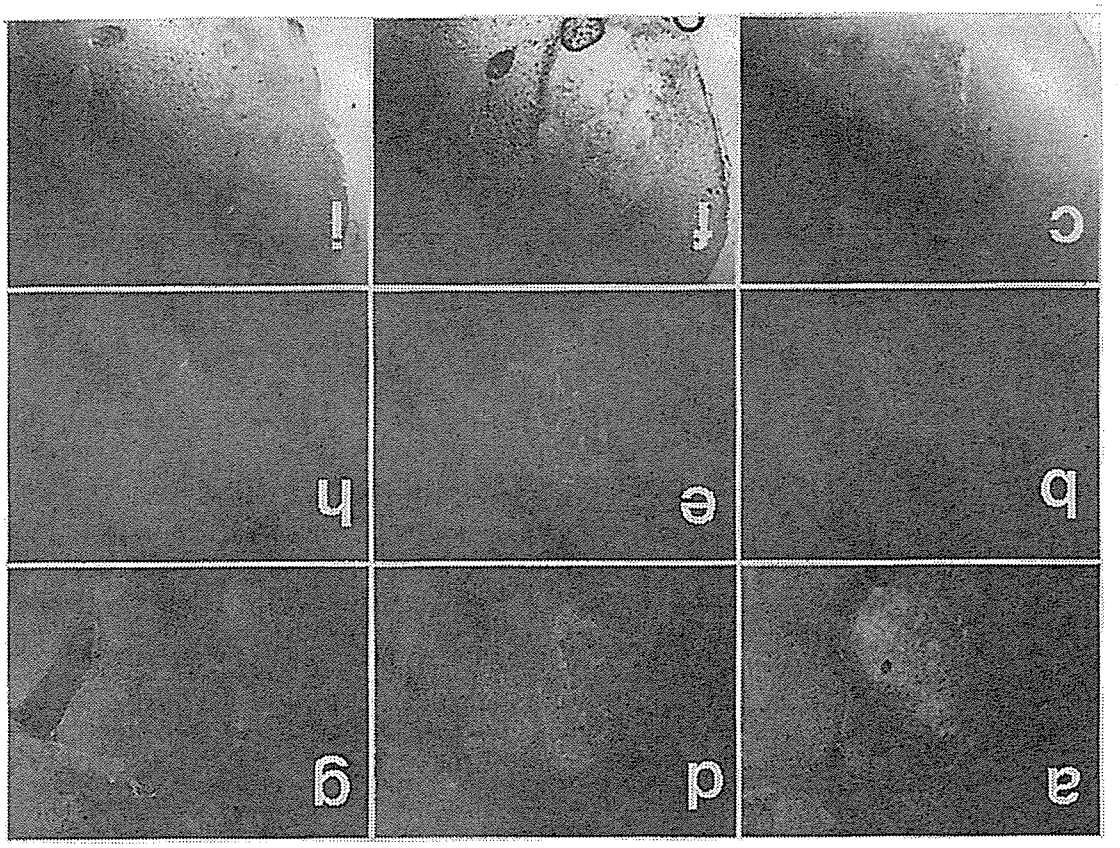

FIG. 2. Images demonstrating survival in the ischemic brain of transplanted neurospheres made from mouse ESCs 2 weeks after transplantation (a–c), 4 weeks after transplantation (d–f), and in sham controls (g–i). Red indicates NeuN (a, d, and g); green, GFP (b, e, and h). The GFP-positive cells occupied the ischemic areas (a–f), especially 4 weeks after ischemia (d–f). Interference differential microscopic images (c, f, and i) demonstrate the area of infarction, which was located in the lateral striatum after ischemia (c and f). Original magnification × 40.

shown in Fig. 2, surviving cells occupied a small area (Fig. 2g–i). Infarct volumes were not significantly different between the specimens prepared 2 weeks after ischemia and those 4 weeks after ischemia (data not shown).

Differentiation of Transplanted ESC-Derived NPCs

At 4 weeks after transplantation, GFP-positive cells demonstrated mature neuronal morphological features (Fig. 3a). In addition, we investigated the expression of both the differentiation markers and the various neurotransmitters (Fig. 3 and Table 2). Transplanted cells were immunopositive for NeuN (Fig. 3b), TuJ1, and GFAP (Fig. 3c). Of the GFP-positive cells, 60 ± 10% were NeuN-positive, 40 ± 10% TUJ1-positive, and 22 ± 7.2% GFAP-positive. Only 0.4 ± 0.5% of the GFP-positive cells were GalC-positive. Next we examined neurotransmitter expression of the transplanted cells. Of the GFP-positive cells, 33.3 ± 11.5% were GAD-positive (Fig. 3d), 13.3 ± 5.8% glutamate-positive (Fig. 3e), 2.1 ± 2.5% TH-positive (Fig. 3g), 1.8 ± 2% serotonin-positive (Fig. 3h), and 0.4 ± 0.2% ChAT-positive (Fig. 3e) cells.

TABLE 1

*Occupied area of transplanted cells in the brain**

Group	% of Hemisphere Occupied
controls	4.0 ± 1.2
2 weeks postischemia	18.8 ± 2.5
4 weeks postischemia	26.5 ± 4.0

* Data are expressed as the means ± standard deviation.

Discussion

In this study, we generated multipotential NPCs from ESCs and transplanted them into ischemic mouse brain. These cells could survive and expand widely in the ischemic area. Moreover, the transplanted NPCs differentiated into various types of neural cells.

TABLE 2

*Differentiation of transplanted cells in the ischemic brain**

Marker	% GFP
NeuN	60.0 ± 10.0
TuJ1	40.0 ± 10.0
GFAP	22.0 ± 7.2
GalC	0.38 ± 5.3
TH	0.6 ± 0.36
GAD	33.3 ± 11.5
Glutamate	13.3 ± 5.8
Serotonin	0.5 ± 0.44
ChAT	0.4 ± 0.2

* Data are expressed as the means ± standard deviation.

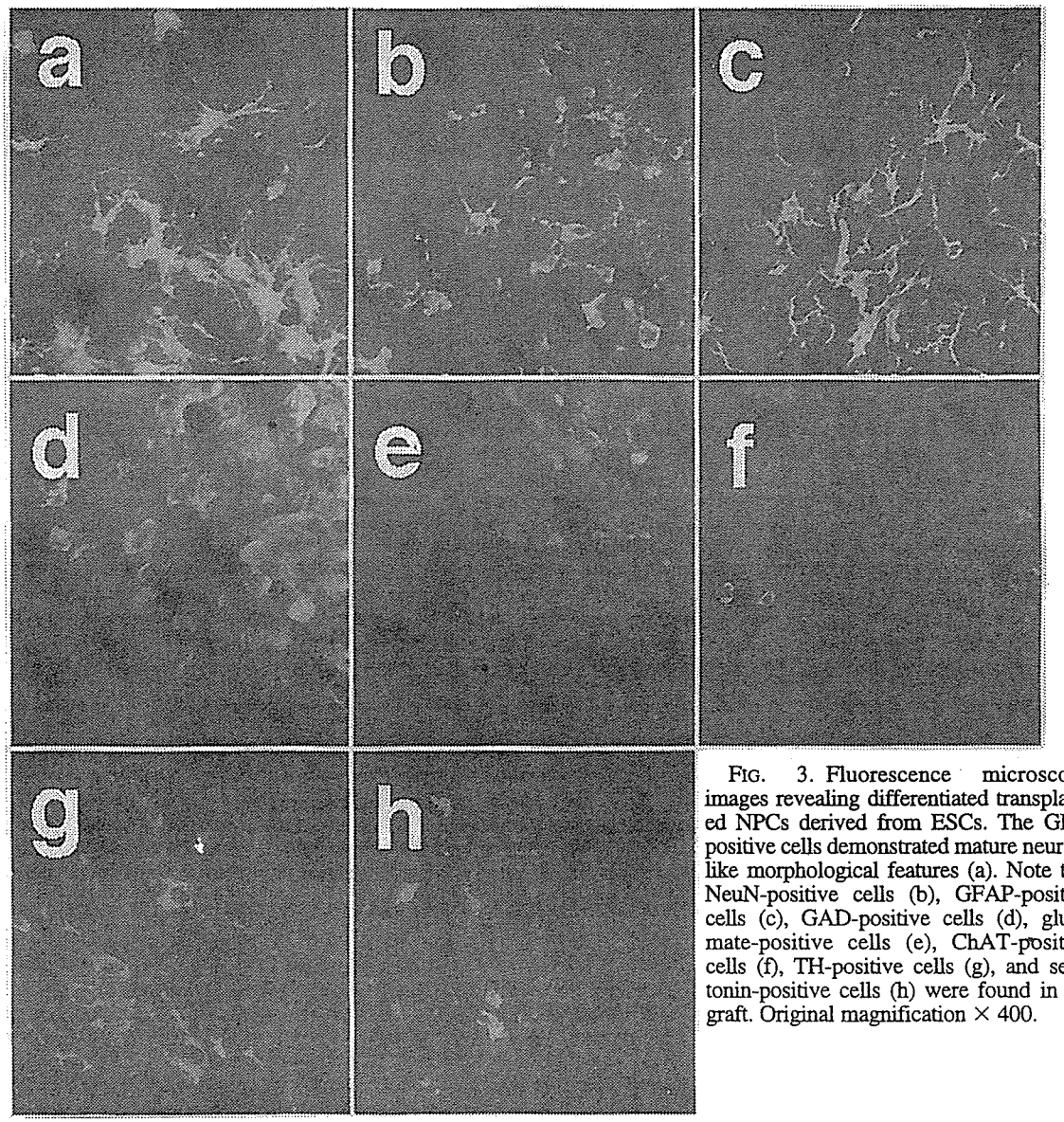

FIG. 3. Fluorescence microscopy images revealing differentiated transplanted NPCs derived from ESCs. The GFP-positive cells demonstrated mature neuron-like morphological features (a). Note that NeuN-positive cells (b), GFAP-positive cells (c), GAD-positive cells (d), glutamate-positive cells (e), ChAT-positive cells (f), TH-positive cells (g), and serotonin-positive cells (h) were found in the graft. Original magnification × 400.

Embryonic stem cells have many characteristics required for an optimal source for cell replacement therapy.[4] The ESCs are self-renewing, multipotent cells derived from the inner cell mass of the preimplantation blastocyst.[4] Kawasaki and colleagues[12] previously reported a strong neuralization-inducing activity present on the cell surface of stromal cells and named it "SDIA." In the absence of exogenous BMP4, mouse ESCs were shown to differentiate efficiently into NPCs and neurons when cultured on SDIA-possessing mouse stromal cells (PA6 cells) for 1 week.[12] Recently, the SDIA method has also become applicable for primate ESCs. After having been cultured on PA6 cells for 2 weeks, the majority of primate ESC colonies contained a large number of NPCs and postmitotic neurons.[12] Neural progenitor cells have multipotent, self-renewing capacities and can be cultured as neurospheres.

In this study, we analyzed several neurotransmitters' expressions. Note that GAD is a γ-aminobutyric acid synthetic enzyme. The γ-aminobutyric acidergic neurons in the cerebellum are rich in ventral mesencephalon or Purkinje cells. Choline acetyltransferase is a synthetic enzyme of acetylcholine. Cholinergic neurons are rich in the basal forebrain and associated with Alzheimer disease. Glutamate is used by descending pathways originating from neocortical pyramidal cells. The dorsal raphe nucleus is known to be rich in serotonin, which is implicated in emotion, fear, and cognition. Dopaminergic neurons of the substantia nigra are lost because of Parkinson disease. Tyrosine hydroxylase expression is linked to the secretion of levadopa, which is a dopamine precursor.[25,27,30] To determine cell types, we used several markers. Beta-Tubulin-III is expressed in postmitotic neunrons at an early stage of development. The NeuN is a nuclear protein that is a marker of a mature neuron. Both GalC and CNPase are thought to be mature oligodendrocyte markers. As an astrocyte marker, GFAP is detectable during fetal glial development.[2]

The use of neural transplantation for the treatment of neurological diseases first became a potential therapeutic modality in 1979 when Bjorklund and colleagues[5,13,24] demonstrated that implanting dopaminergic-containing neurons

into the rat striatum improved functional deficits induced by damage to the nigrostriatal pathway. Since then, advances in neural transplantation have moved from the animal model to the human model, with varying degrees of success.[11,19,20,23,29] In the animal models, authors examined a wide variety of disease states—from degenerative diseases to trauma and stroke—and the tissues used for transplantation—from fetal tissue to tumor lines to stem cells.[19,20,23,26,29] In some models, implants provide a source of neurotrophic factors.[6,7,15] Successes in animal models have led to transplant trials in the human population. Patient trials have been focused on transplantation for Parkinson disease, Huntington disease, spinal cord injury, and stroke.[4,13] As research in animal models progresses, transplant trials may be initiated for the treatment of multiple sclerosis, traumatic brain injury, cerebral palsy, amyotrophic lateral sclerosis, Alzheimer disease, and other disorders.[4,13,26]

In patients disabled by stroke, the concept of restoring function by transplanting human neuronal cells into the brain is a novel one. Data obtained from a rat model of transient focal cerebral ischemia demonstrated that transplantation of fetal tissue restored both behavioral and motor functions.[17,19,20,29] As for studies in humans, Kondziolka and colleagues[14,18] reported the results of a clinical trial using human neuronal cells. In examining 12 patients in this trial, their initial objective was to demonstrate the safety and feasibility of the neuronal cell implantation procedure. Among the treatment groups, mean National Institutes of Health Stroke Scale total scores decreased and mean European Stroke Scale total scores increased—both changes indicating improvement.[14,18] The transplanted cells were proposed to have improved neurological function through a number of different mechanisms, including provision of neurotrophic support, production of neurotransmitters, reestablishment of local interneuronal connections, cell differentiation and integration, and improvement of regional O_2 tension.

In the present study, we used ESC-derived NPCs for transplantation. The advantage in ESCs is that they can be expanded easily compared with neural stem cells. We also confirmed the differentiation of ESC-derived NPCs. During ischemia, various types of neurons as well as glial cells and oligodendrocytes are lost. The ESCs could supply these cells. Interestingly, in the sham-operated control brains, the transplanted cells occupied only a small area. On the contrary, in the ischemic brain, the transplanted cells spread throughout the ischemic lesion. This result indicates that the fate of the graft is dependent on the host environment. After ischemia, several cytokines and growth factors are known to be released. Today, the family of growth and trophic factors has been proposed to affect the survival and development of neuroprogenitor cells. Among them, LIF and ciliary neurotrophic factor in addition to more traditional growth factors, such as platelet-derived growth factor, are considered to be potent promoters of neuroprogenitor cell proliferation and their eventual differentiation.[1,22] Moreover, brain-derived neurotrophic factor, another member of the neurotrophin family (which includes nerve growth factor, neurotrophin-3, and neurotrophin-4/5), was shown to have great potency in modulating the growth and survival of dopaminergic cells and their precursors.[1,22] Glial-derived neurotrophic factor has similar or even enhanced trophic effects on dopaminergic neurons and their precursors.[1,22]

In using a 30-minute ischemia model, we did not examine behavioral improvement after transplantation, because such a model demonstrates only a slight behavioral deficit, thus making it difficult to assess behavior. Therefore we will use a longer period of ischemia in the next study and will examine network formation.

Conclusions

In summary, we confirmed the survival and differentiation of ESC-derived NPCs transplanted into the ischemic brain. We used the SDIA method on murine ESCs. Note that this method is also effective on primate and even human ESCs. Our findings indicated that ESC-derived NPCs can function in the brain.

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18. 内頸動脈閉塞例に対して頭蓋内-外バイパス術は有効な方法か

1 序論

内頸動脈・中大脳動脈の慢性的な閉塞・狭窄が原因で灌流域末梢の脳血流が低下し，脳梗塞をきたす血行力学的脳虚血に関しては，脳梗塞の再発予防として脳血流を術直後より増加させることの可能なバイパス術が理論的には有効であろうと考えられてきた．

2 指針

「73歳以下，症候性で発症から3カ月以内，日常生活が自立している（Rankin Disability Scale 1，2），脳血管撮影上内頸動脈・中大脳動脈の閉塞あるいは狭窄を認める」症例の中で，「定量法が確立された3次元的脳血流測定法（PET，^{123}I-IMP SPECT，cold Xe CT）で病変側中大脳動脈灌流域の安静時血流量定量値が正常値の90%未満，アセタゾラマイド反応性が10%未満」の時のみ，バイパス術の適応がある．

3 エビデンス

1] EC/IC Bypass Study（N Engl J Med. 1985; 313: 1191-200）[1]

目的：症候性の内頸動脈・中大脳動脈閉塞狭窄症をもつ症例において致死的あるいは非致死的脳梗塞の再発をバイパス術は減少させるという仮説を検証．平均追跡期間は56カ月．

対象：症候性で発症から3カ月以内，脳血管撮影上内頸動脈・中大脳動脈の閉塞あるいは狭窄を認める1,377例．北米，ヨーロッパ，本邦も含んだアジアの症例を対象．

治療：薬物治療群（714例）：アスピリン325 mg/日．外科治療群（663例）：アスピリン325 mg/日に加え，浅側頭動脈あるいは後頭動脈と中大脳動脈皮質枝の開頭吻合術．

結果：致死的あるいは非致死的脳梗塞の再発率，死亡率，登録時症候側半球の脳梗塞再発率など，すべての項目で両群間に有意差はなかった．

結論：症候性の内頸動脈・中大脳動脈閉塞狭窄症をもつ症例において致死的あるいは非致死的脳梗塞の再発予防に対するバイパス術の有効性はない．

2] JET study（脳卒中の外科．2002; 30: 97-100，脳卒中の外科．2002; 30: 434-7）[2,3]

＊いずれも中間解析

目的：症候性の内頸動脈・中大脳動脈閉塞狭窄症をもつ症例の中で血行力学的脳虚血を呈している症例において，脳梗塞の再発をバイパス術は減少させるという仮説を検証．追跡期間は24カ月．

対象：「73歳以下，症候性で発症から3カ月以内，日常生活が自立している（Rankin Disability Scale 1，2），脳血管撮影上内頸動脈・中大脳動脈の閉塞あるいは狭窄を認める，CT・MRI上広範な皮質梗塞を認めない，定量法が確立された3次元的脳血流測定法（PET，^{123}I-IMP SPECT，cold Xe CT）で病変側中大脳動脈灌流域の安静時血流量定量値が正常値の90%未満，アセタゾラマイド反応性が10%未満」を満たす206例．本邦の症例のみ対象．

治療：薬物治療群（103例）：アスピリンまたはアスピリンに加えてチクロピジン．外科治療群（103例）：薬物治療に加え，浅側頭動脈と中大脳動脈本幹あるいは皮質枝の開頭吻合術．

結果：Kaplan-Meier analysisによる解析では薬物療法群が外科治療群に比して有意に（$p=0.046$）高い頻度でprimary end pointに達していた．Relative riskは0.354であった．primary end point（脳梗塞再発を含めたすべての原因によるRankin Disability Scale 3，4，5および死亡）に達した症例の原因の内訳は，外科治療群では同側脳梗塞再発以外にプロトコール違反（登録時にすでにRankin Disability Scale 4），心筋梗塞による死亡，腎不全による死亡などであった．薬物療法群では登録時と同じ責任血管が原因の脳梗塞再発によるend pointが主であった．他に，対側半球の脳梗塞および小脳脳幹部梗塞，急性心筋梗塞などであった．secondary endpoint（登録時と同側の脳梗塞再発によるRankin Disability Scale 3，4，5および死亡）においても，Kaplan-Meier analysisによる解析では薬物療法群が外科治療群に比して有意に（$p=0.045$）高い頻度でsecondary endpointに達していた．relative riskは0.270であった．

結論：症候性の内頸動脈・中大脳動脈閉塞狭窄症をもつ症例の中で血行力学的脳虚血を呈している症例において，日常生活の介助を要するほどの脳梗塞の再発予防にバイパス術は有効である．

4 根拠となった臨床研究の問題点と限界

1985年に発表された国際共同研究であるEC/IC Bypass Studyはその研究デザインに対する批判として，多数の登録外での治療例，症例数の不足，研究期間の長期化，多数の不適合例，追跡不能例，不完全な経過観察，周術期合併症の多さ，脳血流からみた適応決定の曖昧さなどがあった[4,5]．最も大きな欠点は患者選択に際し，血行力学的脳虚血の概念が導入されていないことにあった．すなわち，血行力学的脳虚血以外の原因で脳梗塞が再発している症例にはバイパス術は当然無効であり，また，脳主幹動脈閉塞性病変による脳梗塞の発症機序として血行力学的脳虚血は全体の10%前後と少なく，これらが，国際共同研究の結果に影響しているものと考えられた．JET studyはこれらの国際共同研究の批判をふまえ，本邦で組織された研究である．この研究の最大の特徴は，脳循環の測定を定量的に高い精度で行い，血行力学的脳虚血を有する症例のみを対象とすることである．一方，本研究の限界点は「73歳以下，症候性で発症から3カ月以内，日常生活が自立している（Rankin Disability Scale 1，2），定量法が確立された3次元的脳血流測定法（PET，^{123}I-IMP SPECT，cold Xe CT）で病変側中大脳動脈灌流

域の安静時血流量定量値が正常値の90%未満，アセタゾラマイド反応性が10%未満」のときのみ，2年間以内ではバイパス術が有効であるという事実のみであり，これ以外の状況（たとえば75歳で発症からすでに1年以上経過した症例）でのバイパス術の有効性については証明されていない．

5 本邦の患者に適応する際の注意点

JET studyは本邦で行われた研究であるので，このまま適応できる．

6 コメント

JET studyはかなり重症の血行力学的脳虚血を対象にしている．しかし，hospital-basedの研究では脳虚血再発作を有意にきたしやすい閾値はより軽症な血行力学的脳虚血にあるという報告がある[6,7]．現在，薬物療法のみで脳虚血再発作をきたしやすい閾値を本邦でJET 2 studyとして，施行中である．また，北米でもPETを用いた血行力学的脳虚血をもつ症例のみを対象としてバイパス術の有効性を証明しようとする共同研究（Carotid Occlusion Surgery Study: COSS）が進行中である．

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脳梗塞一般
脳梗塞の治療　慢性期の治療

慢性期血行再建術—頸動脈内膜剥離術，浅側頭動脈・中大脳動脈吻合術—

Vascular reconstruction (chronic)—CEA, STA-MCA anastomosis—

西　京子　　宇野昌明　　永廣信治

Key words：血行再建術，頸動脈内膜剥離術(CEA)，バイパス手術，JET study

はじめに

脳主幹動脈である内頸動脈や中大脳動脈(M1)の狭窄や閉塞は，末梢あるいは穿通枝などの血管閉塞と異なり，その広範囲な支配領域から内科治療では脳虚血症状が予防できない場合がある．外科的治療の血行再建術は血行動態を急速に改善することが可能であり，頸動脈内膜剥離術や浅側頭動脈・中大脳動脈吻合術はその代表的なものである．

1. 頸動脈内膜剥離術 (carotid endarterectomy: CEA)

頸動脈分岐部は動脈硬化病変の好発部位であり，脳虚血発作・脳梗塞の責任病巣となり得る．脳虚血を発症する機序としては，高度狭窄により血行力学的血流低下を来す場合と，頸動脈病変(プラーク)の粥腫破綻や付着血栓の遊離が動脈塞栓源となる場合がある．頸動脈内膜剥離術(CEA)は狭窄部位のプラークを摘出することにより狭窄の解除と塞栓源の除去ができ，脳梗塞を予防する治療法であり，脳卒中に対する外科治療の中で唯一有効性が証明されている．

CEAは1953年以後長年の臨床実績があり，症候性頸動脈狭窄症に対しては1991年に発表されたNASCET(North American Symptomatic Carotid Endarterectomy Trial)[1]や1998年のECST(European Carotid Surgery Trial)[2]，無症候性頸動脈狭窄症に対しては1995年のACAS(Asymptomatic Carotid Atherosclerosis Study)[3]などの欧米の大規模なrandomized studyで，脳梗塞の初発・再発予防にCEAは内科的治療よりも有意に勝るという良好な成績があげられている．症候性頸動脈狭窄では，NASCET，ECSTの登録患者の狭窄率別の追跡報告で，どちらも狭窄率70-99％で患側の卒中リスクはCEAで有意に低下している(NASCET: 絶対/相対リスク低下率 19.4％/69％，ECST: 絶対/相対リスク低下率 8.5％/45％)(表1)[4]．

無症候性頸動脈狭窄に対しては1995年に発表されたACASが有名であるが，60％以上の頸動脈狭窄症1,659例の5年間で，患側の卒中の発生率はCEAがわずかに内科治療より有意に少ない結果を示した(CEA 5.1％，内科治療 11.0％：p=0.04)が，CEAによる患側のmajor stroke/deathの絶対リスク減少は有意差が認められなかった(p=0.26)．2004年に無症候性頸動脈狭窄症(1993年-2003年，60％以上の狭窄3,120例)

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